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Full Length Article

Assessment of leptin and resistin levels in non-obese multiple myeloma patients and their relation with Ig level and disease stage

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KEYWORDS

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Abstract *Introduction:* Multiple myeloma (MM) accounts for approximately 0.8% of all cancer diagnoses and 0.9% of cancer deaths. Leptin receptors were expressed on $CD34^+$ cells. Resistin receptors were expressed on inflammatory cells and pro-inflammatory cytokines increase the expression of resistin on monocytes.

Aim of work: To assess the level of leptin and resistin in non-obese multiple myeloma patients and to study their relation with Ig level and disease stage.

Subjects & methods: 32 subjects were included; 16 patients diagnosed with MM and 16 healthy individuals served as control. All were subjected to history taking, clinical examination, routine laboratory investigations and leptin & resistin blood level. Laboratory investigations were done for diagnosis and staging for MM patients.

Results: Leptin was significantly higher in MM patients compared with the control group, unlike resistin which showed no significant difference between the two groups. A significant positive relation was found between IgG level & leptin. Similarly, a significant difference in leptin level has been observed between stage I & stage II (higher in II).

Conclusions: Leptin may play a role in the pathogenesis of MM and its level may be changed in different stages.

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Introduction

Multiple myeloma (MM) is a common hematological malignancy [1]. It accounts for approximately 0.8% of all cancer diagnoses and 0.9% of cancer deaths [2]. MM affects mostly older people with a median age of approximately 70 years. Blacks are more likely to be affected than whites (2:1) and MM is slightly more common in males than females [1].

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Accumulating evidence supports a role for obesity in the etiology of MM [3,4]. As adipose tissue expands in obesity, the amount of anti-inflammatory adipokines, particularly adiponectin, decreases and the amount of pro-inflammatory adipokines with an oncogenic potential, such as leptin, resistin, visfatin and chemerin, and cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6 increases [5]. The evidence from studies showed that apart from energy storing, adipose tissue also acts as an endocrine organ. Preserving the balance between the levels of adipocytokines secreted from adipose tissue is important [6]. Adipokines exert significant effects on metabolism and lipogenesis as well as in regulation of human inflammatory responses [7]. These adipocytokines especially leptin and resistin are widely investigated [8].

Leptin increases the glucose uptake and glucose cycle in cells independent of insulin. Recent studies indicated that leptin is also associated with growth [9]. In vitro cancer studies demonstrated that leptin has mitogenic effects and increases migration and growth factors [10].

The findings that leptin expression can be induced rapidly by inflammatory stimuli such as IL-1 and TNF-α during the acute phase of immune response indicate a role for leptin acting as a mediator in regulating stimulatory capacity on T cells [11]. In monocytes and macrophages, leptin has been shown to stimulate proliferation and phagocytosis, together with production of pro-inflammatory cytokines [12]. Furthermore, leptin has been shown to promote the survival of both T and B lymphocytes by suppressing apoptosis [11,13]. Leptin also increases the production of a variety of proinflammatory cytokines such as IFN-γ and IL-2 in T lymphocytes [14].

Functional leptin receptors are found to be expressed on diverse cancer cells derived from different tissues such as breast, colon or prostate [15–17]. The best evidence that leptin can indeed be involved in neoplastic processes has been provided by studies on breast and colorectal cancer models, while the results for other cancer types are very limited and often inconsistent or inconclusive [18]. Receptors for leptin have been identified in several myeloid and lymphoid leukemic cell lines [19,20].

Resistin is one of white adipose tissue adipocytokines [21]. Plasma resistin levels were reported to be associated with many inflammatory markers [22]. Resistin shares several features with proinflammatory cytokines and can play a role in the regulation of inflammation and immunity [23]. The majority of epidemiologic studies had indicated that in vivo hyper-resistinemia is associated with some obesity-related malignancies such as colon cancer and prostate cancer [24]. Elevated levels of plasma resistin have been found in females with breast cancer, and higher levels appear related to the highest histological grade [25]. Furthermore, resistin levels are significantly higher in lymphoma patients than in patients with other hematological malignancies [26]. Although only a few studies have analyzed resistin in patients with malignancies, the general properties of resistin could contribute to tumorigenesis [27]. Thus, the distinct possibility exists that obesity may be linked to MM through altered secretion of one of these adipokines [26,28].

So, the aim of this current study was to assess leptin and resistin levels in non-obese multiple myeloma patients and study their relation with Ig level and disease stage.

Subjects and methods

The present study was carried out on 32 subjects selected from out-patient's clinic & in-patient's wards of the Internal Medicine Department (Hematology unit), Tanta University Hospital, from 10/2011 until 10/2013.

All patients were initially diagnosed before taking treatment. All participants provided written informed consent. The subjects of this study were classified into two groups.

Group 1

It included 16 patients with histopathologically confirmed multiple myeloma according to World Health Organization (WHO) diagnostic criteria for symptomatic multiple myeloma [29], 6 males & 10 females, their ages ranged from 51 to 61.5 years (55.7 ± 3.47). Eight patients were in stage I and 8 patients were in stage II, according to the Durie–Salmon staging [30]. None of the patients were in stage III. All patients were MM IgG.

Group 2

It included 16 healthy subjects as a control group of matching age and sex, 6 males & 10 females; their ages ranged from 50 to 61 years (55.46 ± 3.98).

Inclusion criteria

Newly diagnosed patients histopathologically confirmed multiple myeloma according to WHO diagnostic criteria for symptomatic multiple myeloma.

Exclusion criteria

Patients or controls with: documented infection within the last 2 weeks, hypertension, diabetes, hyperlipidemia, obesity (body mass index [BMI] > 24.9), or insulin resistance state (using homeostatic model assessment of insulin resistance [HOMA-IR] formula) (to eliminate the effect of those factors on leptin and resistin levels). Patients with febrile neutropenia, sepsis, any organ failure (kidney, liver, lung, heart) were excluded.

Methods

All patients and controls were subjected to the following: Full history taking, complete clinical examination, routine laboratory investigations including: complete blood count (CBC), serum total cholesterol, HDL, LDL & triglycerides, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), LDH, liver and kidney function tests and serum leptin and resistin using enzyme-linked immunosorbent assay (ELISA)[31,32]. MM patients were diagnosed according to

WHO Diagnostic criteria [29]; they were classified according to the Durie–Salmon staging system [30]. All blood specimens were collected prior to the initiation of chemotherapy or blood transfusions for the patient's group.

Leptin by ELISA method [31]

Serum leptin level was measured using the enzyme-linked immunosorbent assay method ELISA (R&D system Poston Biochem, 840 Memorial Dravee, Cambridge). The sensitivity of the assay was 7.8 pg/ml. The intra-assay coefficient of variation was 3.1%, while the inter-assay coefficient of variation was 4.3%.

Resistin by ELISA method [32]

Serum resistin level was measured using the enzyme-linked immunosorbent assay method ELISA (R&D system Poston Biochem, 840 Memorial Dravee, Cambridge). The sensitivity of the assay was 0.055 ng/ml. The intra-assay coefficient of variation was 4.7%, while the inter-assay coefficient of variation was 8.4%.

Statistical analysis

Comparisons between cases and controls were conducted by using chi-square test for categorical variables and Mann Whitney test for comparing means. Spearman correlation test was used to examine the relations of both leptin and resistin, and metabolic characteristics.

P value less than 0.05 was considered statistically significant. All analyses were performed using SPSS statistical software (SPSS V.16, Inc., Chicago, IL).

Results

The current work included 16 patients diagnosed with MM; 6 males (37.5%) & 10 females (62.5%); their ages ranged from 51 to 61.5 years (55.7 ± 3.47). According to the Durie–Salmon staging, 8 patients were in stage I & 8 patients were in stage II. None of the patients were in stage III. All patients were MM IgG.

The control group included 16 healthy subjects, 6 males (37.5%) & 10 females (62.5%), their ages ranged from 50 to 61 years (55.4 ± 3.98). MM cases and controls were matched by gender and age.

MM cases had significantly higher levels of ESR 1st hour ($P < 0.0001$) and LDH ($P < 0.0001$) in comparison to control subjects. Leptin levels of controls were significantly lower than that of MM cases ($P < 0.0001$), on other hand, no significant difference was found in resistin level between MM cases and control ($P = 0.438$), (Table 1).

In MM patients, we found a significant positive correlation between leptin level and IgG level ($P = 0.017$). However, no relation had been detected between leptin level & Plasma cell% ($P = 0.81$). Regarding resistin, we could not find any relation between its level and IgG level or plasma cell% in MM ($P = 0.79$ and 0.323), respectively (Table 2 and Fig. 1).

We also found a significant difference in leptin level in different grades of MM, as leptin was significantly higher in grade II ($P = 0.032$) in comparison to grade I (Table 3). On the contrary, resistin showed no significant difference in its level in grades I and II ($P = 0.937$) (Table 3).

Regarding ESR 1st hour and LDH levels in MM, both demonstrated a significant positive correlation with leptin level ($P = 0.029$ and 0.002, respectively) (Table 4 and Figs. 2 and 3).

On the other hand, LDH had a significant negative correlation with resistin level ($P = 0.047$), while ESR showed no significant correlation with resistin level ($P = 0.534$) (Table 4 and Fig. 4).

Table 2 Relation between leptin and resistin with both IgG level & Plasma cell% in MM patients.

	Leptin		Resistin	
	Spearman *r*	*P* value	Spearman *r*	*P* value
IgG	0.585	0.017	−0.102	0.79
Plasma cells	−0.092	0.81	−0.406	0.323

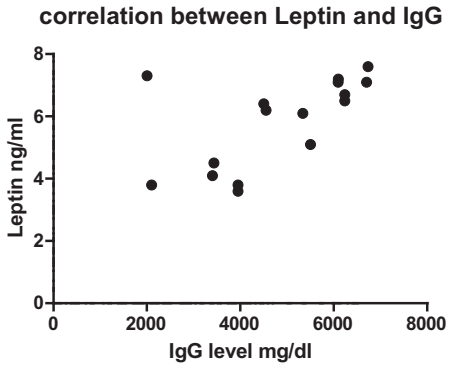

Figure 1 Correlation between leptin level and IgG level in MM patients.

Table 1 Descriptive characteristics of patients with multiple myeloma ($n = 16$) and controls ($n = 16$).

Character	MM patients $n = 16$	Control $n = 16$	*P* value
Sex M/F	6/10	6/10	$P = 1$
Age in years mean ± SD	55.7 ± 3.47	55.46 ± 3.98	$P = 0.609$
ESR 1st hour mm mean ± SD	81.5 ± 13.64	8.75 ± 1.65	$P < 0.0001$
LDH (U/L) mean ± SD	395 ± 67.63	273.13 ± 69.45	$P < 0.0001$
Leptin ng/ml mean ± SD	5.82 ± 1.43	2.16 ± 0.72	$P < 0.0001$
Resistin ng/ml mean ± SD	1.56 ± 0.74	1.6 ± 0.68	$P = 0.438$

Table 3 Comparison between LEPTIN and resistin levels in stages I and II in MM patients.

	MM stage	Mean	SD	*P* value
Leptin	Stage I	4.62	1.1	0.032
	Stage II	6.74	0.81	
Resistin	Stage I	1.53	0.85	0.937
	Stage II	1.47	0.62	

Table 4 Correlation of leptin and resistin levels with both ESR and LDH in MM patients.

	Leptin		Resistin	
	Spearman *r*	*P* value	Spearman *r*	*P* value
ESR 1st hour	0.544	0.029	−0.148	0.534
LDH	0.705	0.002	−0.501	0.047

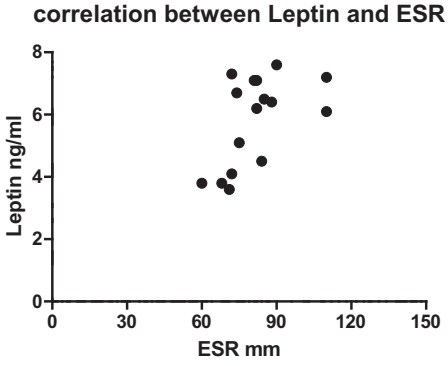

Figure 2 Correlation between leptin and ESR in MM patients.

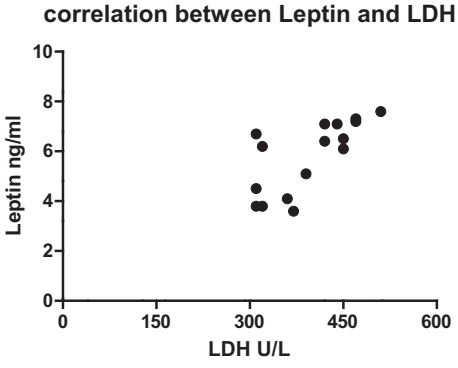

Figure 3 Correlation between leptin and LDH in MM patients.

Discussion

Leptin is an important regulator of caloric intake and energy expenditure, and recent studies have linked obesity to a dysregulated leptin metabolism [33]. Modulating adipokines could be particularly an attractive goal for cancer prevention. Regular moderate exercise, adoption of a balanced diet, weight reduction and bariatric surgery for morbidly obese persons may

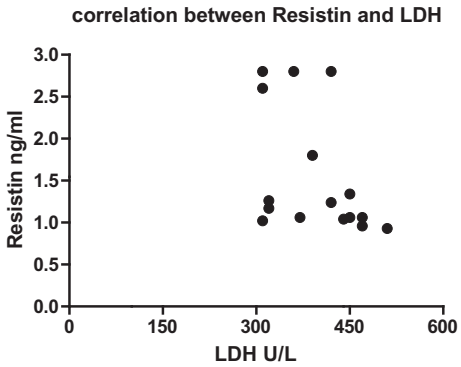

Figure 4 Correlation between resistin and LDH in MM patients.

increase plasma adiponectin [34], and decrease plasma leptin, resistin, reducing thus the risk of developing cancer. Very recently, L-4F, an apolipoprotein peptide mimetic used for the pharmacologic upregulation of adiponectin, decreased multiple myeloma (MM) tumor burden through induction of apoptosis, increased survival of myeloma-bearing mice and provided protection against myeloma destructive osteolytic bone disease, an important clinical feature of MM [35].

In the present study, we investigated the following: the level of leptin & resistin in non obese patients with MM; the relation of leptin & resistin with other parameters in MM such as ESR and LDH, and the relation between leptin & resistin levels with the staging of MM and IgG level.

As regards leptin & multiple myeloma (MM), we found that the level of the leptin was significantly higher in the MM patients when compared with the control group ($P < 0.0001$).We also found a positive significant correlation between IgG level & leptin in MM patients ($P = 0.017$), on other hand, there was no significant relation between bone marrow plasma cells % & leptin ($P = 0.81$). Moreover, we found a significant difference in leptin level between stage I & stage II in MM patients (the level was higher in stage II) ($P = 0.032$). Regarding ESR 1st hour and LDH levels in MM, both had a significant positive correlation with leptin level ($P = 0.029$ and 0.002, respectively).

The results in this work were partially in accordance with those of Alexandrakis et al. [28] who found that leptin was significantly higher in the newly diagnosed MM patients than in controls. However, the authors disagreed with us when they added that; leptin did not increase with advancement of the disease stage, and concluded that, Leptin serum levels do not reflect disease severity in MM.

Our results were also in agreement with those of Pamuk et al. [26] who found that mean leptin levels in MM patients were significantly higher than in the control group. Reseland et al. [36] similarly found that Plasma leptin concentrations were significantly higher in the newly diagnosed patients compared with the healthy control group.

Although Dalamaga et al. [37] found that MM patients tend to have higher mean leptin levels than controls by univariate analysis, which may reflect their higher degree of obesity. Then they reported that after adjusting for age, gender, and BMI, as well as for multiple comparisons performed, serum leptin levels were not significantly different between MM patients and controls. The rest of their results were in accordance

with ours as they stated that Leptin was positively associated with LDH. Leptin levels were also significantly different among multiple myeloma stages. Higher stages tend to present higher levels of leptin .The differences in mean leptin levels by stage were not small.

Similarly, in a recent study carried out by Hofmann et al. [38], the authors found that patients with MM had higher level of leptin (10.01 ± 2.64) in comparison to control (9.6 ± 2.71) but not reaching a statistically significant level. And they added that, Leptin levels were not associated with MM risk.

Resistin was originally discovered as a molecule that induced insulin resistance and caused hyperglycemia without affecting peripheral insulin sensitivity [13]. However, data in humans are controversial. In contrast to mice, resistin in humans is expressed in lower levels in adipocytes but at relatively higher levels in circulating blood monocytes [39]. Moreover, studies in humans have failed to detect higher serum resistin levels in obese or insulin resistant subjects [40]. It is not known if resistin can influence bone marrow hematopoietic activity or immune responses, but the resistin gene is highly expressed in bone marrow and leucocytes, indicating a probable regulatory role in hematopoiesis [41].

As regards resistin & MM, we found that the level of the resistin was lower in the MM patients when compared with the control group but not reaching a significant level ($P = 0.438$). Also, we found insignificant correlation between IgG levels & resistin in MM patients ($P = 0.79$). The same was found in the relation between bone marrow plasma cells % & resistin in MM patients which was insignificant ($P = 0.323$). As regards staging in MM patients, we found insignificant difference in resistin level between stage I & stage II, ($P = 0.937$). Only LDH had a significant negative correlation with resistin level ($P = 0.047$).

The above mentioned results were in keeping with those of Reseland et al. [36] who could not detect any significant differences in the plasma concentrations of resistin between MM patients and controls.

Similar results were obtained by Pamuk et al. [26] who also reported that the mean resistin levels in MM patients were insignificantly higher than the control group.

In contrast, the above-mentioned data contradicted with those of Dalamaga et al. [37] who found that the resistin levels of control subjects were significantly higher than levels of case subjects ($P < 0.0001$). The authors also recorded that insignificantly different resistin levels were found among different prognostic stages and paraprotein classes.

The difference between our results & the others could be attributed to the difference in the number of the patients; moreover some authors did not consider selecting their patients based on the exclusion of the causes that could make a difference in the leptin & resistin level such as obesity and hyperlipdemia.

In summary, the results of our study suggest that leptin and not resistin may play a role in the pathogenesis of MM through its possible systemic effect, microenvironment, receptor & gene expression, immunological changes & angiogenesis. Also Leptin blood levels may be changed in MM patients with different stages.

Agents that reduce cancer cell proliferation in conjunction with high circulating levels of leptin should be evaluated for use in the prevention and treatment of cancer [42].

Yet, several enigmatic issues involving resistin receptor and signaling pathways remain to be clarified in order to unmask its ontological role in cancer pathophysiology [43].

However the limitations of this study include: small sample size, lack of multivariate regression models adjusting for several variables, determinations of IL-6, and determination of adiponectin.

Conclusion

Further studies are needed to investigate the possible prognostic and therapeutic value of leptin and resistin in clinical practice of patients with MM.

Conflict of interest

I declare that I do not have any financial relationships with any industry through employment, consultancies, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit either directly or through immediate family.

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